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HSM-01006

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DATE: July 3, 2001

SUBJECT: BRAND NAME: Monitor
ACTIVE INGREDIENT: Methamidophos
COMPANY NAME: Mobay Chemical Corporation
TRACKING I.D. NUMBER: 128195 - E
RECORD NUMBER (RN): 92476
DATA PACKAGE NUMBER (DPN): 315-123
EPA REGISTRATION NUMBER: 3125-0-
TITLE: The Percutaneous Absorption of Methamidophos (SX-1757) in Male
Rats

Chevron Environmental Health Center, Inc. conducted a dermal absorption study of methamidophos in male Sprague-Dawley[®] rats. This study was initiated on June 16, 1987. Sample analyses were completed on July 16, 1987 and the study was completed on January 18, 1991. The study was performed in compliance with the U.S. EPA FIFRA Good Laboratory Practice Standards (40 CFR Part 160), except inspection of the in-life portion of the study was not conducted by the Quality Assurance Unit of Chevron. A summary of this dermal absorption study and the evaluation of the results are presented below.

A. Preparation of Animals

Thirty six male Sprague-Dawley[®] rats (CrI:CD (SD)[®]BR) were used in this study. The animals were approximately 50 days old and the weights ranged from 241 - 317 grams. After receiving, animals were quarantined for 13 days. The rats were randomly allocated to 3 dose groups and within each dose group the animals were further subdivided into 3 exposure time groups consisting of 4 rats each. Food and water was available ad libitum during the course of the study. All rats were housed in individual stainless steel cages with wire-mesh floors prior to dosing. The room conditions were: 12-hour light/dark cycle, temperature ranged from 68 – 71 °F and humidity ranged from 62 to 66%. The application site (dorsal trunk) was clipped on the day prior to dosing. Approximately one hour before dosing, the application site was shaved free of hair with disposable razor and washed with mild soap and water to remove sebaceous gland secretions. A neoprene rubber template was glued to the back of each rat with cyano-acrylate glue, defining a 2.5 x 4-cm application site. After dermal application of the test material, rats

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were placed individually in Metrap[®] restraining metabolism chambers for their respective exposure times. Air from the metabolic cages was exhausted through a CO₂ trap (~150 ml 0.5N NaOH) and a volatile trap (activated charcoal).

B. Preparation and Administration of the Doses

[S-methyl-¹⁴C]-Methamidophos was obtained from Mobay Chemical Corporation and purified by thin-layer chromatography to 99.8%. Appropriate amounts of Monitor[®] technical (SX-1757, 81.4% methamidophos) was added to [S-methyl-¹⁴C]-methamidophos to get concentrations of 40, 4 and 0.4 µCi/mg methamidophos. Deionized water was added to obtain final concentrations of approximately 1, 10 and 100 mg/mL dosing solution. Homogeneity of the dosing solution was verified before dosing. The three groups of rats were dosed as follows: Group I = 0.05 mg/rat (average 5 µg/cm²), Group II = 0.5 mg/rat (average 49 µg/cm²), and Group III = 5.0 mg/rat (average 486 µg/cm²). The test material was vortexed immediately before dosing each animal. Approximately, 50 µL of the dosing solution was applied to the application site of each animal with a VWR Digital Microdispenser. The exposure times were 2, 10 and 24 hours.

C. Sample Collection and Analysis

At the end of the exposure period, the animals were anesthetized with an intraperitoneal injection with sodium pentobarbital. The application site was vigorously scrubbed three cycles (times) with a two-inch square, 12-ply gauze pad, which was immersed in 0.5% soap solution and squeezed before scrubbing, followed by one scrubbing with deionized water alone. The skin of each rat was excised around the template. The skin was separated from the template and each was analyzed separately. A small strip of skin around the periphery of the template was also excised. Samples collected for the analysis were soap/water scrubs, acetone skin rinse, methanol template rinse, treated-skin residues, blood, urine, feces, carcass, methanol cage rinse, CO₂ trap (NaOH solution) and volatile trap (activated charcoal). The radioactivity in the prepared samples was analyzed using a Beckman LS-9800 or LS-5801 liquid scintillation counter.

D. Results

The mean recoveries of radioactivity as percent of administered dose for the three dose groups and exposure/sacrifice times are shown in Tables 1, 2 and 3. The treated-skin residue is considered absorbed unless bioavailability of the residue can be determined using the exponential saturation model (Thongsinthusak *et al.*, 1999). The estimated dermal absorption was calculated as percent of the applied dose found in the treated skin, blood, urine, feces, carcass, cage rinse, carbon dioxide trap and volatile trap. The estimated dermal absorption values are shown in those Tables. The mass balance, especially for 10- and 24-hour exposures for the low dose (5 µg/cm²), is too low and is not acceptable. The low recovery was likely due to poor trapping efficiency of volatile ¹⁴CO₂ or other metabolites. Also, improper handling and analysis of samples could possibly result in low recovery.

Table 1. Mean recoveries of radioactivity (% dose) in rats topically administered with ¹⁴C-methamidophos at 0.05 mg/rat (average 5 ug/cm²).

Exposure time (h)	Soap/water scrubs	Acetone skin rinse	Template rinse	Skin residue	Blood**	Urine	Feces**	Carcass	Cage rinse	CO2 trap	Volatile trap	Total
2	60.0	10.2	0.9	13.7	0.1	0.5	0.1	1.9	0.2	1.1	0.1	88.8
	<i>Dermal absorption* = 17.7</i>											
10	37.3	12.8	1.4	6.2	0.1	1.2	0.1	2.8	0.3	1.2	0.4	63.8
	<i>Dermal absorption* = 12.3</i>											
24	33.3	11.2	1.6	14.1	0.0	1.2	0.2	2.5	0.4	0.5	0.8	65.8
	<i>Dermal absorption* = 19.7</i>											

* Unadjusted (% administered dose in skin residue+blood+urine+feces+cacass+cage rinse+co2 trap+volatile trap) **0.1 is used instead of <0.1 shown in the report for three values

Table 2. Mean recoveries of radioactivity (% dose) in rats topically administered with ¹⁴C-methamidophos at 0.5 mg/rat (average 49 ug/cm²).

Exposure time (h)	Soap/water scrubs	Acetone skin rinse	Template rinse	Skin residue	Blood	Urine	Feces**	Carcass	Cage rinse	CO2 trap	Volatile trap	Total
2	62.8	11.2	1.4	5.8	0.1	0.3	0.1	2.9	0.2	1.1	0.1	86.0
	<i>Dermal absorption* = 10.6</i>											
10	35.3	14.3	1.4	13.4	0.2	2.0	0.2	4.6	0.4	1.5	0.4	73.7
	<i>Dermal absorption* = 22.7</i>											
24	22.3	14.0	2.1	18.7	0.1	3.2	0.3	4.9	0.3	0.8	0.7	67.4
	<i>Dermal absorption* = 29.0</i>											

* Unadjusted (% administered dose in skin residue+blood+urine+feces+cacass+cage rinse+co2 trap+volatile trap) **0.1 is used instead of <0.1 shown in the report for one value

Table 3. Mean recoveries of radioactivity (% dose) in rats topically administered with ¹⁴C-methamidophos at 5 mg/rat (average 486 ug/cm²).

Exposure time (h)	Soap/water scrubs	Acetone skin rinse	Template rinse	Skin residue	Blood	Urine	Feces**	Carcass	Cage rinse	CO2 trap	Volatile trap	Total
2	69.0	6.5	0.8	3.4	0.2	1.8	0.1	4.5	0.3	1.3	0.0	87.9
	<i>Dermal absorption* = 11.6</i>											
10	39.8	11.6	0.8	9.4	0.1	9.8	0.4	6.0	0.7	2.7	0.1	81.4
	<i>Dermal absorption* = 29.2</i>											
24	29.1	13.1	1.5	12.2	0.1	8.4	0.5	5.8	0.7	1.0	0.5	72.9
	<i>Dermal absorption* = 29.2</i>											

* Unadjusted (% administered dose in skin residue+blood+urine+feces+cacass+cage rinse+co2 trap+volatile trap) **0.1 is used instead of <0.1 shown in the report for one value

E. Discussion and Recommendation

Recoveries of the administered doses for different exposure times ranged from 63.8% to 88.8%. Generally, the recovery should be on the order of 85% or greater. An important factor that could cause the low recovery was because [S-methyl-¹⁴C]-methamidophos was used instead of [³²P]-methamidophos. A significant portion of volatile compounds might have not been accounted for. Some other factors could also contribute to a low recovery.

The report revealed that Monitor[®] technical (SX-1757, 81.4% methamidophos) was mixed with [S-methyl-¹⁴C]-methamidophos in deionized water to prepare the dosing solution. If in fact, SX-1757 is the technical material (no other surface active agents), the dosing solution is not appropriate. Typically, a formulation blank should be added to the dosing solution (Zendzian, 1994). The report did not disclose other compositions of SX-1757 since it contains 81.4% methamidophos.

The report indicates that Bayer Corporation discussed with and endorsed by the U.S. EPA to add the percent unrecovered dose (presumably untrapped volatile metabolites) to the percent systemic absorption (not include the treated-skin residue) to obtain a conservative estimate of percent dermal absorption. This method of estimation of the dermal absorption is not scientifically defensible because an unrecovered dose may be due to the handling or analytical process. In order to obtain an acceptable recovery, methamidophos must be labeled at the core of the molecule, i.e. using [³²P]-methamidophos instead of [S-methyl-¹⁴C]-methamidophos.

Results from this study will not be used to estimate the dermal absorption of methamidophos for the pesticide exposure assessment process.

References:

- Thongsinthusak, T., Ross, J. H., Saiz, S. G., and Krieger, R. I. 1999. Estimation of dermal absorption using the exponential saturation model. *Reg. Toxicol. Pharmacol.* 29:37-43.
- Zendzian, R. P. 1994. Dermal Absorption of Pesticides. Pesticide Assessment Guidelines. Subdivision F, Hazard Evaluation: Human and Domestic Animals. Series 85-3. Health Effect Division, Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C.

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(Dermal/Tamaron-Rats; HSM-01006)